IMPACT OF GRADE ≥2 PNEUMONITIS (G2+ PNS) ON PATIENT REPORTED OUTCOMES (PROS) WITH DURVALUMAB (D) AFTER CHEMORADIOTHERAPY (CRT) IN UNRESECTABLE STAGE III NSCLC

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Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

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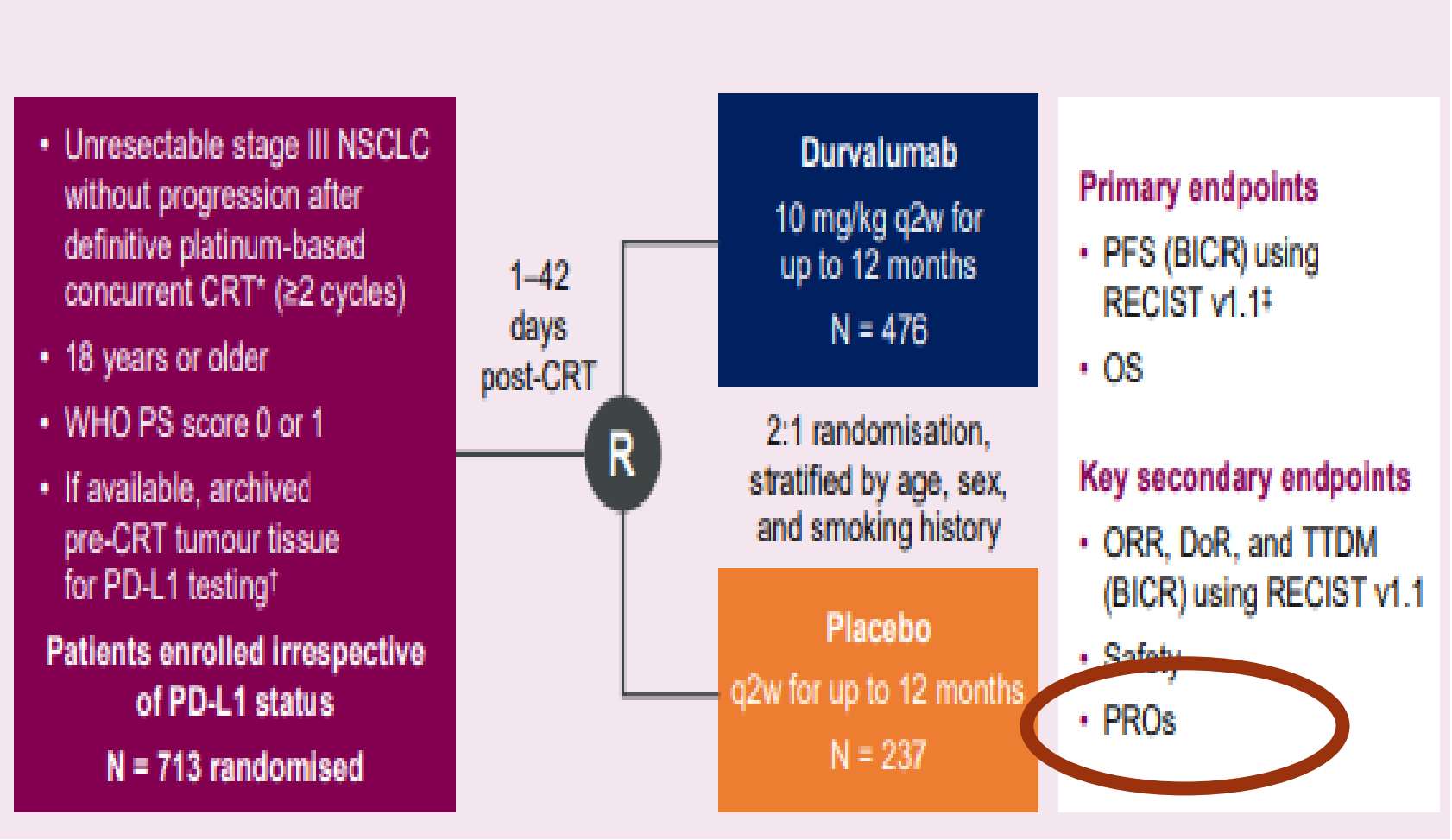

Poster 118P

Impact of grade ≥2 pneumonitis on patient-reported outcomes (PROs) with durvalumab after chemoradiotherapy (CRT) in unresectable stage III NSCLC

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Objective

- To assess the effect of on-study grade ≥2 pneumonitis on PROs with durvalumab in the PACIFIC trial.

Conclusions

- In PACIFIC, grade ≥2 pneumonitis was more common with durvalumab (19.7%) versus placebo (13.9%) and typically occurred within 3 months of starting treatment.
  - A prior exploratory analysis suggested treatment benefit with durvalumab was maintained regardless of the occurrence of pneumonitis.[7]
- PRO results indicate that durvalumab did not have a detrimental impact on patient QoL compared with placebo, irrespective of whether patients experienced grade ≥2 pneumonitis.
- These findings indicate that the possibility of grade ≥2 pneumonitis should not deter physicians from using the PACIFIC regimen in eligible patients; treatment guidelines should be followed if this AE occurs.

Plain language summary

Based on the findings of the PACIFIC study,[1,2] durvalumab (an immunotherapy drug) is approved for patients with stage III non-small-cell lung cancer when surgery is not an option, provided they have completed both chemotherapy and radiotherapy (chemoradiotherapy) without their cancer progressing.[5,6] Pneumonitis (lung inflammation) is a common complication of radiotherapy and can also be a side effect of immunotherapy. In the PACIFIC study, a higher proportion of patients experienced pneumonitis with durvalumab (33.9%) compared with placebo (24.8%).[2] We aimed to investigate whether the occurrence of grade ≥2 pneumonitis (i.e., pneumonitis presenting with clinical symptoms) during the study impacted the tolerability of durvalumab from a patient perspective.

Patient-reported outcomes, including symptoms, functioning, and health-related quality of life (QoL) were scored using questionnaires completed at several timepoints throughout the study. During the study, grade ≥2 pneumonitis (including pneumonitis related to previous radiotherapy) occurred in 19.7% of patients assigned to durvalumab and 13.9% of patients assigned to placebo. Grade ≥2 pneumonitis typically occurred within 3 months of starting durvalumab or placebo. No clinically meaningful changes in scores for patient-reported outcomes were observed at Weeks 16 or 24 (from the start of treatment) among patients assigned to durvalumab or placebo, regardless of whether they experienced grade ≥2 pneumonitis. Moreover, the amount of time patients spent without experiencing a worsening of their health-related QoL was longer with durvalumab compared with placebo, which remained the case when adjusting for the occurrence of grade ≥2 pneumonitis.

In summary, up to 12 months of durvalumab therapy, administered following chemoradiotherapy, did not have a detrimental impact on patient QoL compared with placebo, irrespective of whether patients experienced grade ≥2 pneumonitis.

Poster | Plain language summary | Supplementary material

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please click on the link below.
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Background

- In the Phase 3 PACIFIC trial, up to 12 months of durvalumab therapy significantly improved OS and PFS (the primary endpoints) versus placebo in patients with unresectable stage III NSCLC and no progression following concurrent CRT.[1,2]
- Durvalumab had a manageable safety profile and did not detrimentally affect PROs (symptoms, functioning, and global health status/QoL) compared with placebo.[1-3]
- Based on these findings, which were recently reinforced by updated survival analyses with ~5 years of follow-up,[4] the PACIFIC regimen (durvalumab after platinum-based CRT) became a new standard of care for patients with unresectable stage III NSCLC.[5,6]
- Most patients in PACIFIC experienced at least one AE (durvalumab 96.8%; placebo 94.9%);[1,2] any-grade pneumonitis (including radiation-pneumonitis) was among the most common, occurring in 33.9% and 24.8% of patients with durvalumab and placebo, respectively.[2]
  - Pneumonitis predominantly occurred with low-grade severity,[2] and a prior exploratory analysis from PACIFIC suggested treatment benefit with durvalumab was maintained regardless of the occurrence of pneumonitis.[7]
- With broad application of the PACIFIC regimen, there is a need to better understand the impact of pneumonitis, particularly grade ≥2 (i.e., symptomatic) pneumonitis, on PROs with durvalumab.

Methods

Trial Design

- PACIFIC (NCT02125461) was a Phase 3, randomised, double-blind trial of adult patients with WHO PS 0/1 and no disease progression following concurrent CRT (**Figure 1**).
- Patients with unresolved grade >2 toxicities (CTCAE v4.03), or grade ≥2 pneumonitis, from prior CRT were excluded. More details of the trial design are published elsewhere.[2]

Figure 1. PACIFIC Trial Design (NCT02125461)

*Radiation dosage typically 60–66 units of gray in 30–33 fractions. †Using the Ventana SP263 immunohistochemistry assay. ‡Defined as the time from randomisation until the date of objective disease progression or death by any cause in the absence of progression.

Assessments

- Pneumonitis was investigator assessed (CTCAE v4.03) and defined as focal or diffuse inflammation of the lung parenchyma – diagnoses of acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis, alveolitis, diffuse alveolar damage, and radiation-pneumonitis were included.
  - Institutional standards in serologic, immunologic, and histologic testing were recommended in the protocol to rule out other possible aetiologies.
  - On-study pneumonitis was defined as a *de novo* event occurring on study Tx, or a pre-existing grade 1 event that worsened during the study, and ≤90 days following the end of study Tx or before starting subsequent anticancer Tx (whichever occurred earlier).
- PROs were assessed with paper-based questionnaires (EORTC QLQ-C30 [v3] and QLQ-LC13) administered at the time of random assignment to study Tx (baseline), Week 4, Week 8, every 8 weeks until Week 48, then every 12 weeks until progression.[3]
  - The last assessment for patients who discontinued study Tx because of progression was Day 30 after the final dose of study Tx.

Statistical Analysis

- This exploratory, *post hoc* analysis was based on the ITT population and used the data cut-off for the primary analysis of OS (22 March 2018).
- Incidence and timing of on-study, grade ≥2 pneumonitis was summarised with descriptive statistics.
- Changes in PRO scores from baseline were summarised according to the presence/absence of on-study, grade ≥2 pneumonitis (for all PROs prespecified as longitudinal endpoints of interest in the original ITT analysis[3]).
  - A clinically meaningful difference was defined as a ≥10-point increase (worsening for symptoms; improvement for functioning and global health status/QoL) or decrease (improvement for symptoms; worsening for functioning and global health status/QoL).[8]
  - Changes in scores were assessed at Weeks 16 and 24 to reflect the typical timeframe of pneumonitis occurrence in PACIFIC.
- Confirmed TTD with durvalumab versus placebo for pre-specified and post-hoc PROs of interest was analysed using multivariable Cox models adjusted for the time-dependent occurrence of on-study, grade ≥2 pneumonitis. Two sets of covariates were used to account for possible correlation of grade ≥2 pneumonitis with baseline factors:
  - *Model 1* (*base model*): trial stratification factors (age, sex, and smoking history).
  - *Model 2*: the base model + additional baseline prognostic factors.

Results

Patients and Grade ≥2 Pneumonitis

- As of 22 March 2018, 94/476 (19.7%) and 33/237 (13.9%) randomly assigned patients experienced on-study, grade ≥2 pneumonitis in the durvalumab and placebo arms, respectively (median follow-up 25.2 months; range 0.2–43.1).
  - Grade 3/4 pneumonitis was uncommon in PACIFIC, occurring in 3.4% and 3.0% of patients who received durvalumab and placebo, respectively.[9]
- Baseline characteristics for the subgroups of patients who did and did not experience on-study, grade ≥2 pneumonitis are summarised in the supplementary appendix (see supplement, accessible via the **QR code**).
- Most patients experienced grade ≥2 pneumonitis within 90 days of starting durvalumab (76/94; 80.9%) and placebo (26/33; 78.8%).
  - Median time to onset was 53.5 days (range 2–406) with durvalumab and 55.0 days (range 14–253) with placebo.
  - Median time to resolution or death was 57.5 days (range 2–588) with durvalumab and 52.0 days (range 4–186) with placebo.

EORTC QLQ-C30 and QLQ-LC13 Compliance Rates

- At the majority of timepoints, compliance rates remained >70% from baseline through Week 48 for both EORTC questionnaires regardless of assigned study Tx and the occurrence of on-study, grade ≥2 pneumonitis (**Figure 2**).
  - Compliance rates were generally lower among patients who experienced grade ≥2 pneumonitis (vs those without grade ≥2 pneumonitis) from Week 8 onward in both the durvalumab and placebo arms.

Changes in Scores for Prespecified PROs at Weeks 16 and 24

- Consistent with the ITT analysis,[3] PRO scores remained stable over time (i.e., <10-point change in mean score vs baseline) in both the durvalumab and placebo arms, regardless of the occurrence of grade ≥2 pneumonitis (**Figure 3**).
  - No clinically relevant (≥10-point) between-arm differences in the mean changes in scores from baseline were observed at Week 16 or Week 24 for any of the analysed PROs, irrespective of the occurrence of grade ≥2 pneumonitis.

Confirmed TTD for PROs of Interest

- For all analysed PROs, confirmed TTD was consistent with the ITT results in both covariate models used to adjust for the time-dependent occurrence of grade ≥2 pneumonitis, with similar HRs and overlapping 95% CIs (**Figure 4**).
- No important differences in TTD of physical functioning (C30), cough (LC13), or dyspnoea (LC13) were observed with durvalumab versus placebo in either of the models (i.e., the HR 95% CIs crossed 1). Meanwhile, TTD was longer with durvalumab in both covariate models for the following:
  - Global health status/QoL (C30)
    - *Model 1*: HR 0.72 (95% CI 0.57–0.91)
    - *Model 2*: HR 0.70 (95% CI 0.56–0.89)
  - Chest pain (LC13)
    - *Model 1*: HR 0.74 (95% CI 0.57–0.95)
    - *Model 2*: HR 0.74 (95% CI 0.56–0.96)
  - Haemoptysis (LC13)
    - *Model 1*: HR 0.62 (95% CI 0.45–0.86)
    - *Model 2*: HR 0.59 (95% CI 0.43–0.83)

Figure 2. Compliance with EORTC QLQ-C30 and QLQ-LC13 by Grade ≥2 Pneumonitis Status

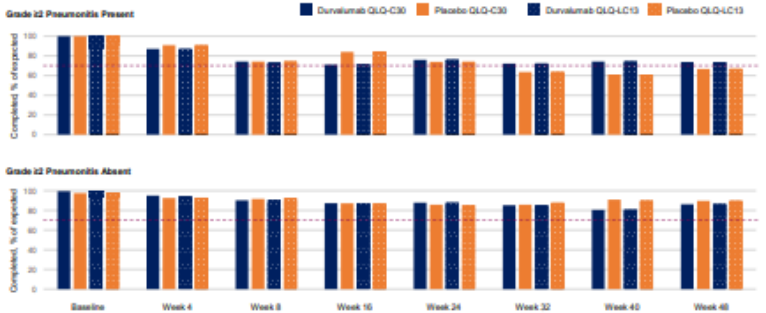


Figure 3. Changes in Scores for Prespecified PROs at Weeks 16 and 24 (from Baseline)

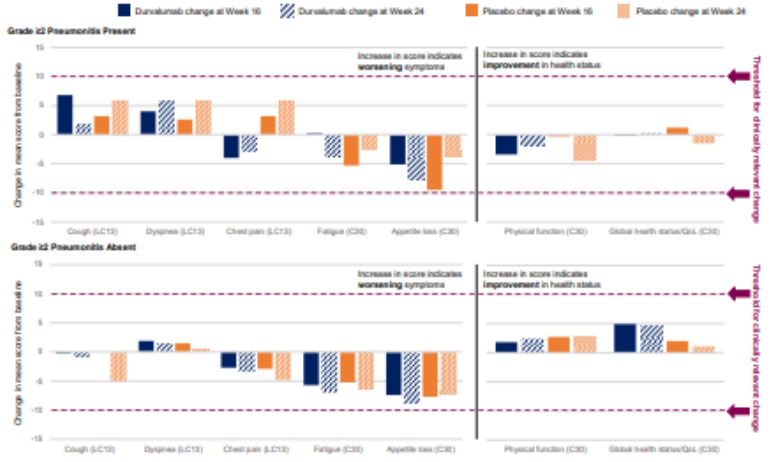
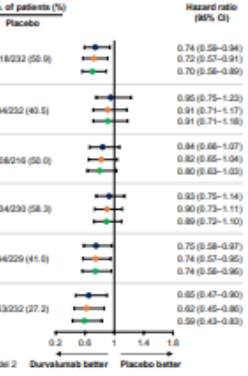


Figure 4. Confirmed TTD for PROs of Interest Adjusted for Time-dependent Grade ≥2 Pneumonitis



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Disclosures

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Abbreviations

AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CRT, chemoradiotherapy; CTCAE v4.03, Common Terminology Criteria for Adverse Events v4.03; C30, Core-30; DoR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; ITT, intent to treat; LC13, Lung Cancer-13; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PRO, patient-reported outcome; PS, performance status; QLQ, quality-of-life questionnaire; QoL, quality of life; q2w, every 2 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors v1.1; TTD, time to deterioration; TTDM, time to death or distant metastasis; Tx, treatment; WHO, World Health Organization; wk, Week.

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BACKGROUND

- Concurrent chemoradiation is the preferred treatment modality in Stage III Non small cell lung cancer.
- Median OS of 18-30 months
- 5year survival of 20-30%

- Unmet need in terms of survival for most of these patients
- Radiation pneumonitis is dose limiting toxicity in patients undergoing chemo radiation
- Most study had V20<35% as cut off

Objectives- To assess the effect of grade ≥2 pneumonitis on PROs with Durvalumab in the PACIFIC trial.

Aim- Investigate whether the occurrence of grade ≥2 pneumonitis during the study impacted the tolerability of Durvalumab from a patient perspective

- **Included**
  - Mean dose to the lung was less than 20 Gy,
  - The V20 (the volume of lung parenchyma that received 20 Gy or more) was less than 35%, or both

- **Excluded**
  - Grade 2 or higher pneumonitis from previous chemoradiotherapy

Assessments

- Pneumonitis was investigator assessed and defined as focal or diffuse inflammation of the lung parenchyma – diagnoses of acute interstitial pneumonitis, interstitial lung disease, pulmonary fibrosis, alveolitis, diffuse alveolar damage, and radiation-pneumonitis were included.
- Serologic, immunologic, and histologic testing were recommended in the protocol to rule out other possible etiologies.
- PROs were assessed with paper-based questionnaires (EORTC QLQ-C30 and QLQ-LC13) administered at the time of random assignment to study Tx (baseline), Week 4, Week 8, every 8 weeks until Week 48, then every 12 weeks until progression.

STATISTICAL ANALYSIS

- This exploratory, post hoc analysis was based on the ITT population
- Changes in PRO scores from baseline were summarized according to the presence/absence of Grade ≥2 pneumonitis.
  - A clinically meaningful difference was defined as a ≥10-point increase (worsening for symptoms) or decrease (improvement for symptoms).
  - Changes in scores were assessed at Weeks 16 and 24 to reflect the typical timeframe of pneumonitis occurrence.

- Two sets of covariates were used to account for possible correlation of grade ≥2 pneumonitis with baseline factors:
  - Model 1 (base model): trial stratification factors (age, sex, and smoking history).
  - Model 2: the base model + additional baseline prognostic factors.

RESULTS

PNEUMONITIS- HOW COMMON

- Most patients in PACIFIC experienced at least one AE (durvalumab 96.8%; placebo 94.9%);
- Any-grade pneumonitis was the most common, occurring in 33.9% and 24.8% of patients with durvalumab and placebo, respectively.
- Grade ≥2 pneumonitis occurred in 19.7% of patients assigned to durvalumab and 13.9% of patients assigned to placebo.
- The most frequent adverse events leading to discontinuation of durvalumab and placebo were pneumonitis (in 6.3% and 4.3%, respectively)

HOW SEVERE

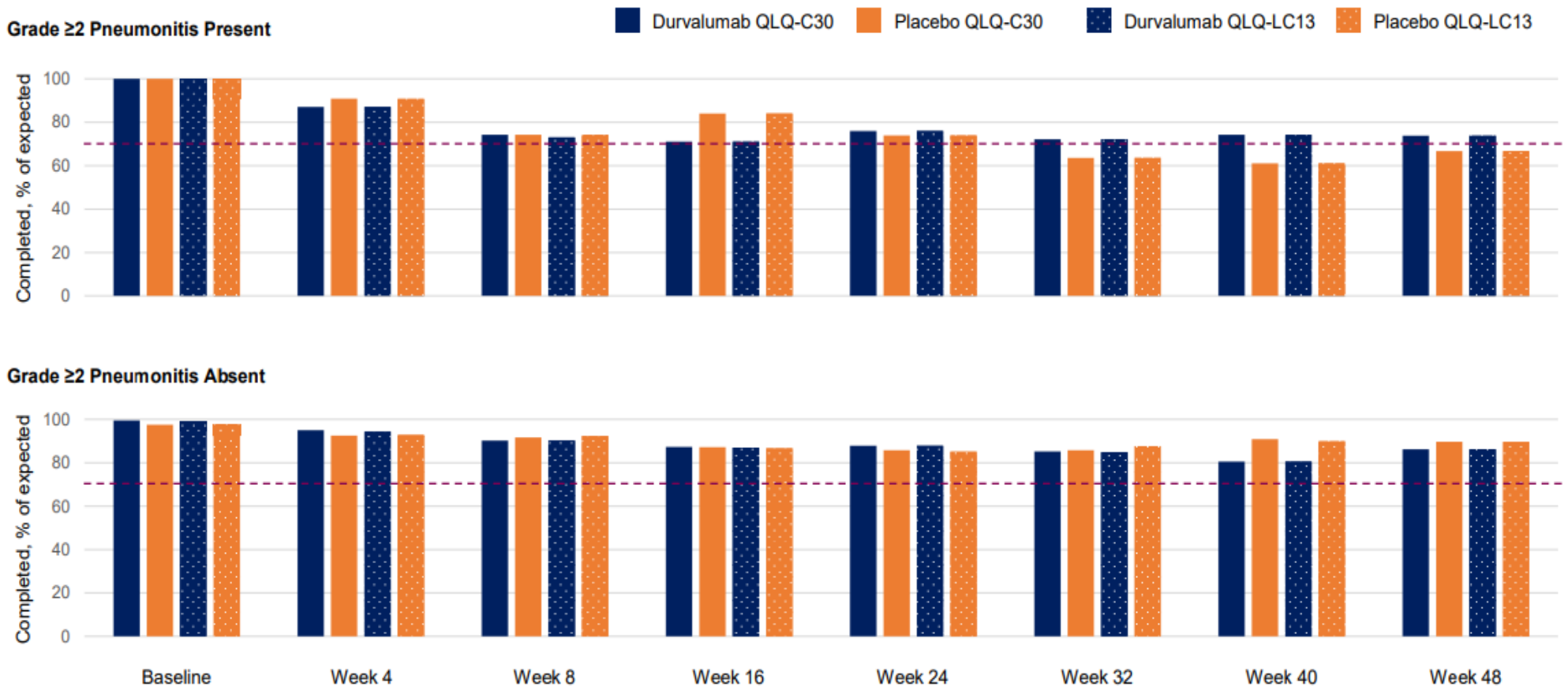
- Grade 1-14.2% and 10.9 (Durvalumab and placebo)
- Grade 2 -16.3% and 10.9% (Durvalumab and placebo)
- Grade 3/4 -3.4% and 3.0% (Durvalumab and placebo)

IMPACT

- Pneumonitis predominantly occurred with low-grade severity, and treatment benefit with Durvalumab was maintained regardless of the occurrence of pneumonitis
- No clinically meaningful changes in scores for patient-reported outcomes were observed at Weeks 16 or 24 among patients assigned to durvalumab or placebo, regardless of whether they experienced grade ≥2 pneumonitis.
- In summary, up to 12 months of durvalumab therapy, administered following chemoradiotherapy, did not have a detrimental impact on patient QoL compared with placebo, irrespective of whether patients experienced grade ≥2 pneumonitis.

COMPLIANCE WITH EORTC QLQ-C30 AND QLQ-LC13

Figure 2. Compliance with EORTC QLQ-C30 and QLQ-LC13 by Grade ≥2 Pneumonitis Status



- At the majority of timepoints, compliance rates remained >70% from baseline through Week 48 for both EORTC questionnaires regardless of assigned study Tx and the occurrence of grade ≥2 pneumonitis

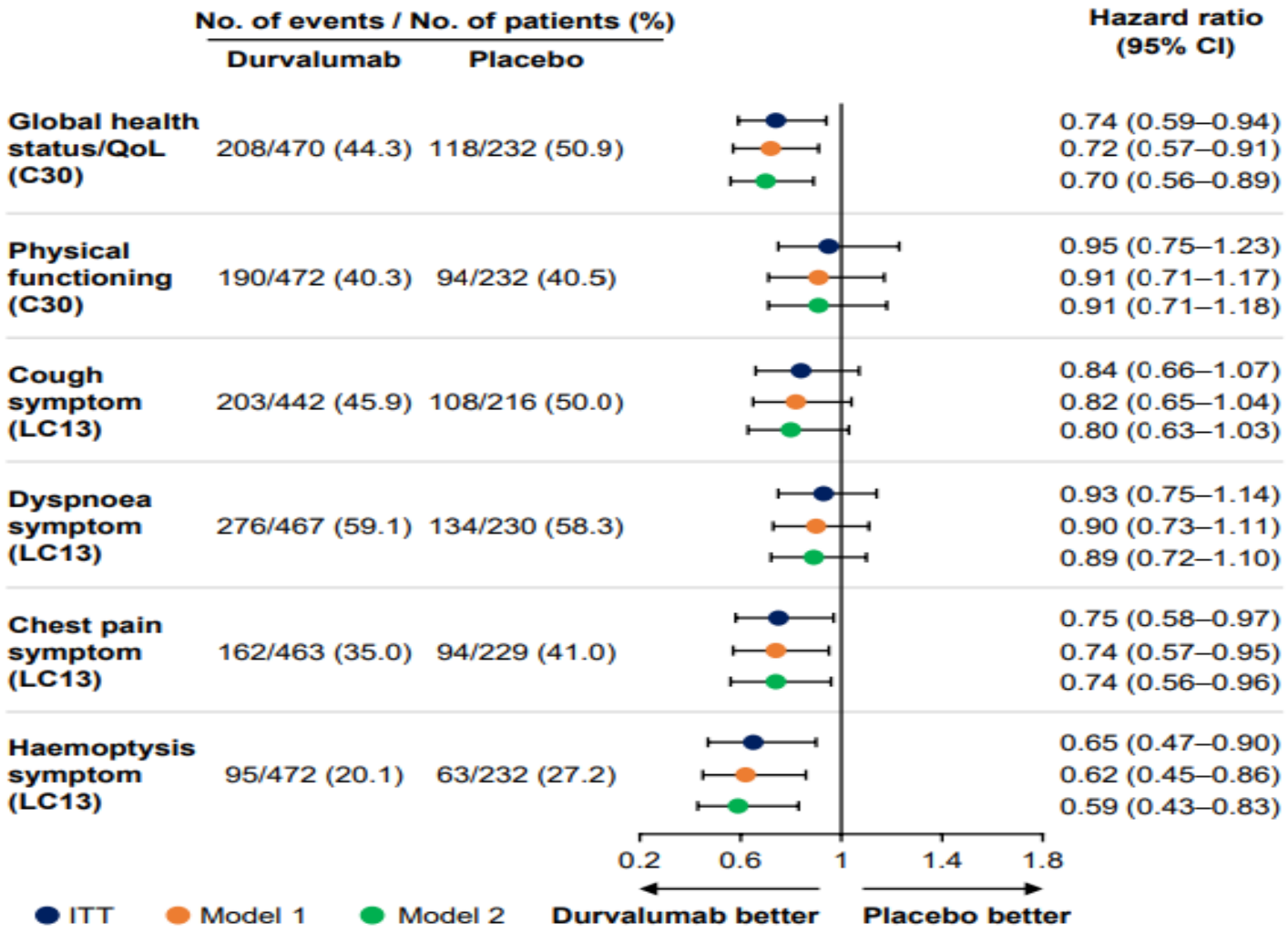
- Compliance rates were generally lower among patients who experienced grade ≥2 pneumonitis (vs those without grade ≥2 pneumonitis) from Week 8 onward in both the durvalumab and placebo arms.

Figure 3. Changes in Scores for Prespecified PROs at Weeks 16 and 24 (from Baseline)

- Consistent with the ITT analysis, PRO scores remained stable over time (i.e <10-point change in mean score vs baseline) in both the durvalumab and placebo arms, regardless of the occurrence of grade ≥2 pneumonitis

- No clinically relevant (≥10-point) between-arm differences in the mean changes in scores from baseline were observed at Week 16 or Week 24 for any of the analysed PROs, irrespective of the occurrence of grade ≥2 pneumonitis

Figure 4. Confirmed TTD for PROs of Interest Adjusted for Time-dependent Grade ≥2 Pneumonitis



- No important differences in TTD of physical functioning (C30), cough (LC13), or dyspnoea (LC13) were observed with durvalumab versus placebo in either of the models
- Meanwhile, TTD was longer with durvalumab in both covariate models for the Global health status/QoL (C30), Chest pain (LC13), Haemoptysis (LC13)

CONCLUSION

- Pneumonitis is dose limiting toxicity in concurrent chemoradiation.
- Addition of Durvalumab adds to toxicity
- But in carefully selected patients (patients without grade 2 or higher pneumonitis post chemoradiation), Durvalumab can be safely administered without compromising survival outcomes and quality of life.